

Short Title: EXTREQOL study results revision

Abstract

Purpose

Delaying progression, ameliorating symptoms and maintaining Quality of Life (QoL) are primary aims of treatment for metastatic Castrate Resistant Prostate Cancer (mCRPC). Real world rather than clinical trial data about symptoms and side effects are sparse. In EXTREQOL patients' QoL, pain and information needs were recorded during treatment.

Methods

Men with mCRPC from 20 UK cancer centres commencing various systemic mCRPC treatments completed QoL, pain and information needs questionnaires at baseline, 3 and 6 months.

Results

132 patients were recruited. Overall QoL declined significantly by 6 months (Functional Assessment of Cancer Therapy-Prostate (FACT-P) mean=-3.89, 95% CI: -6.7 to -1.05, $p = 0.007$; Trial Outcome Index analysis (TOI) mean=-3.10, 95% CI: -5.34 to -0.83, $p = 0.007$). Those who came off novel therapy and remained on LHRH agonist therapy alone had worse scores than patients receiving concomitant chemotherapy (Prostate Concerns Subscale (PSC) mean difference= -4.45, 95% CI: -7.06 to -1.83, p -value=0.001; TOI mean difference = -5.62, 95% CI: -10.97 to -0.26, $p = 0.040$). At 3 & 6 months men who reported pain at baseline improved (43%; 40% respectively), but for others pain levels remained the same (45%; 42%) or worsened (13%; 18%). Information regarding supportive care was lacking throughout the period of time on the study.

Conclusion

Most mCRPC treated patients experience reduced QoL and inadequate pain control. More help with pain management and better information provision regarding supportive care is warranted.

Keywords

mCRPC; pain control; QoL; information needs; side effects

Introduction

Prostate cancer is the most common cancer in UK men [1]. Over the course of the illness many will face multiple treatment options, dependent on the stage of cancer at the time of their diagnosis. Surgical and radiotherapy techniques have improved, and there are more drugs available offering prospects for an extended life of good quality. Unfortunately, for the majority of men presenting with or progressing to advanced (metastatic prostate) disease, the development of metastatic castrate resistant prostate cancer (mCRPC) is inevitable.

Docetaxel chemotherapy became the standard of care for mCRPC patients with good performance status a decade ago following the results of the TAX 327 study [2], and many men remain fit enough to receive further systemic therapy on progression after docetaxel. Cabazitaxel chemotherapy was licensed in Europe in 2011 for use in mCRPC after docetaxel following results of the TROPIC trial [3]. As well as advances in chemotherapy, other treatments have become available including the novel hormone agents, abiraterone acetate (androgen biosynthesis inhibitor), and enzalutamide (androgen receptor antagonist). These compounds have demonstrated significant survival benefits for patients in Phase III clinical trials in the docetaxel naïve setting and also in men who have progressed after chemotherapy [4-6]. In addition, other agents such as radium-223 [7] have also shown improvements in overall survival; the immunotherapies and other agents are under investigation.

The main aims of treatment for mCRPC are to delay progression, ameliorate symptoms and maintain or improve quality of survival. From a patient's perspective, optimal treatment is a trade-off between efficacy and tolerability, and while the increasing number of therapeutic options is welcome, a review of mCRPC clinical trial publications noted that Patient Reported Outcomes (PROs) were either not measured routinely or failed to be reported adequately hampering evaluation [8]. Those with good PRO data showed that enzalutamide compared with placebo significantly improved Quality of Life (QoL) in the AFFIRM trial [9], and in the

PREVAIL trial was associated with a reduced risk of and delayed time to QoL deterioration, pain progression and occurrence of Serious Reportable Events (SREs) [10]. Similarly results from the Phase III COU AA-301 RCT of abiraterone and prednisone versus placebo plus prednisone demonstrated better QoL outcomes for the abiraterone group [11-13]. Beneficial prostate cancer treatment improves QoL through the reduction in symptoms from the cancer itself.

There is an acknowledgement worldwide that the delivery of health care should embrace much more patient participation and involvement as a core element [14]. Pursuant to this, ASCO guidelines for survivors of prostate cancer recommend that an individual's information needs at all stages of disease should be assessed, and that patients are provided with or referred to sources of appropriate information and support resources [15]. While admirable, these goals can be difficult to achieve in under resourced, pressurised hospital clinics. A recent survey of UK Health Care Professionals (HCPs) highlighted the challenges of providing holistic care for men with mCRPC, especially if they require longer consultations to discuss pain management or other supportive care needs [16]. Although limited QoL effects are available from patients participating in clinical treatment trials, also there are few real world data looking at the impact of approved treatments on men or their information needs.

Materials and Methods

Design

EXTREQOL is a six month longitudinal mixed-methods observational study, using questionnaires and interviews to gather views on treatment and care from patients, their partners and UK HCPs [16]. We report here the QoL, information needs and pain relief results of men commencing different treatments for mCRPC. The interview data will be reported separately.

Patients

Twenty hospitals in 19 Trusts in England, Scotland and Wales participated and provided access to men considered suitable for systemic treatment for mCRPC between July 2016

and July 2017. The study was performed in accordance with the Declaration of Helsinki and Ethical approval (16/LO/0403). Sponsorship and all local NHS R&D permissions were obtained for each site.

Standardised questionnaires

Standardised PRO measures were used to examine QoL, pain and information needs. These were the Functional Assessment of Cancer Therapy – Prostate (FACT-P)[17], the Brief Pain Inventory-Short Form (BPI-SF)[18] and the European Organisation for Research & Treatment in Cancer (EORTC)- Quality of Life information needs (INFO25)[19]. Patients recorded their current mCRPC treatment and other concurrent medication on the QoL record and pain relief medication in the section on the BPI-SF at each time point.

Treatment records

Information was provided by the clinical team about the treatments discussed at the decision-making consultation, if a clinical trial was an option, the site of metastasis, and whether or not it was the first presentation of mCRPC. Researchers did not have direct access to patient records for any other details such as medical history, co-morbidities, performance status or prior treatments. However, life expectancy of >6months was a study eligibility criteria.

Procedures

Eligible patients were identified and initially approached by a member of the Multidisciplinary Team (MDT) treating them who briefly explained the QoL study. Those interested completed an expression of interest form providing their contact details. This was faxed to the researchers who called patients approximately 24 hours later to answer any questions, and confirm whether or not they wanted to participate. Written consent was obtained prior to participation. Ethical approval was granted by the London - Surrey Borders Research Ethics Committee 16/LO/0403 on the 22nd March 2016.

Statistical methods

The proportion of patients who either worsened, remained the same or improved at 3 or 6 months with respect to baseline, for the FACT-P scales and single items for pain (GP4, P1,

P2 and P3) were calculated. Additionally, a longitudinal analysis of the scores was undertaken based on linear-mixed effects models for the FACT-P total scores and subscales. A Trial Outcome Index (TOI) score was calculated comprising Physical and Functional Wellbeing plus the Prostate Concerns Subscale (PCS). The TOI is an efficient and common endpoint used in clinical trials, because it is responsive to change in physical/functional outcomes. All models included a random intercept to account for the correlation among scores collected from the same participant. The models included age, partner status, treatment type (chemotherapy, abiraterone, enzalutamide, LHRH agonist therapy alone, radium, trials, other or none) and whether this was the first presentation of mCRPC at baseline, as explanatory variables. Time varying explanatory variables included, period of observation to examine changes over time (3m and 6m) with respect to baseline, whether the participant was on treatment and whether they changed treatment during the previous period of observation.

The “worst pain” scores from the BPI-SF were employed for the pain severity analyses. A score of ≤ 4 is considered no or mild pain and a score of >4 is considered moderate or severe pain. [18] An additional seven items on the BPI-SF measure pain interference and a clinically meaningful change (CMC) in pain severity is defined as a ≥ 2 -point change (increase or decrease) from baseline [20]. The proportion of patients whose pain or interference either worsened, remained the same or improved at 3 or 6 months with respect to baseline were calculated.

Patients’ information needs produce a Global Score (Max Total is 100) for comparison across time and data were summarised using two plots displaying the proportions of “Quite a bit/ Very much” answers to questions 31-49 of the INFO25 at baseline and 6 months. A linear mixed-effects model for FACT-P was fitted to measure the association between information needs being met at baseline and changes in satisfaction and QoL.

The statistical analyses were undertaken using R [21] and the package lme4 [22].

Results

Recruitment

132 patients who were receiving LHRH agonist therapy and diagnosed as mCRPC were recruited, and 33/132 participated in the interview sub study (reported separately). Despite eligibility criteria of life expectancy >6months, 10 men died, 14 were too ill to continue and 2 withdrew for other reasons (Figure 1). 84% of men had bone metastases, see Table 1 for patient characteristics.

Sixty-one men remained on the same treatment throughout the study, and 49 changed treatment at least once. In the first period (baseline to 3 months) treatments received were cabazitaxel (n= 7), docetaxel (n=28), abiraterone (n=20), enzalutamide (n=48), radium 223 (n=18), dexamethasone (n=6), bicalutamide (n=1), the ProCAID trial (docetaxel + AZD5363 / docetaxel alone) (n=1), the PEACE III trial (radium + enzalutamide / enzalutamide alone) (n=1), and the Keynote trial (pembrolizumab + docetaxel + prednisone) (n=1). By TP3 21/106 (19.8%) were on LHRH agonist therapy alone, having previously received docetaxel (n=5), cabazitaxel (n=1), abiraterone (n=2), dexamethasone (n=1), enzalutamide (n=3), and Radium -223 (n=7) One patient never started a new treatment and one man remained on bicalutamide for 6 months.

Quality of Life

Table 2 shows the proportion of patients where QoL scores declined, improved or remained the same from baseline to 3 and 6 months for the FACT-P total, PCS, TOI and the FACT-G. For the group overall there was a significant decline at 6 months on the FACT-P (mean=-3.89, 95% CI: -6.7 to -1.05, p =0.007); on the FACT-G (mean=-3.45, 95% CI: -5.53 to -1.36, p =0.002) and on the TOI (mean=-3.10, 95% CI: -5.34 to -0.83, p =0.007). See Figure 2. QoL mean scores were significantly higher (better) in older men on all scales; the mean difference in score for a ten-year difference in age between two individuals was 1.8 (95% CI: 0.26 to 3.35, p=0.022), 7.7 (95% CI: 3.45 to 12.03, p<0.001), 5.91 (95% CI: 2.84 to 8.89, p<0.001) and 5.82 (95% CI: 2.48 to 9.16, p=0.001) for PCS, FACT-P, FACT-G & TOI respectively. Other studies have shown similar differences with age [23].

The linear mixed effects model revealed significant differences at 6 months on the PCS and TOI for patients receiving different treatment types. Those who came off a newer treatment

and were on LHRH agonist therapy alone had worse scores than those on concomitant chemotherapy (PCS mean difference= -4.45, 95% CI: -7.06 to -1.83 p-value=0.001; TOI mean difference = -5.62, 95% CI: -10.97 to -0.26, p =0.040). Patients presenting with mCRPC for the first time compared with others had higher (better) scores on the TOI (mean difference= 6.74, 95% CI: 0.75 to 12.72, p =0.028). On the FACT-P, responses to the single item GP4 “I have pain” showed improvements for some from baseline (22% at 3 months; 29% at 6 months), and also for P1 “I have aches and pains that bother me” (29%; 33% respectively). The majority either remained the same or worsened.

Pain

At baseline 23% (29/126) reported no pain, 32% (40) reported mild pain and 45% (57) moderate to severe pain on the BPI. Clinically meaningful changes (CMC) in pain severity were calculated from baseline across time and patients categorised as those with none or little pain (n=69), and those experiencing moderate /severe pain (n=57) at baseline (Tables 3a and 3b). Table 4 shows the pain relief medication reported at each time point. Only 15 men did not require analgesia throughout the study. Sixty percent were taking a combination of drugs, for example opioids and paracetamol, but some paracetamol/ibuprofen alone. Five had palliative radiotherapy and none received denosumab or zoledronic acid.

At baseline only 38.5% (22/57) of those with moderate / severe pain experienced $\geq 70\%$ pain relief from their analgesia. This dropped to 37.5% (15/40) at 3 months and 36.5% (15/41) at 6 months.

Information provision

The baseline and 6 month plots for INFO25 are shown in Figures 3a and b. There was no improvement in information provision for any of the areas. The mean (sd) Global score at baseline was 58.49 (18.57), and the mean change at 6m was -1.01 (95% CI: -3.57 to 1.57, p=0.44).

The linear mixed effects model for FACT-P showed significant between- and within- person differences of the global information score on QoL. Higher Global information scores were associated with a better QoL. The mean difference in FACT-P for a ten-point difference in information score at baseline between two individuals was 3.53 (95% CI: 1.86 to 5.20, $p<0.001$). The mean change in FACT-P for a ten-point increase in information score for an individual was 3.56 (95% CI: 1.60, 5.51, $p<0.001$).

Discussion

The findings from the EXTREQOL study showed that overall QoL deteriorated significantly across time for this group of men. The majority (84%) had bone metastases, and almost a fifth (18%) were lost to follow up due to death or sickness. One of the aims of mCRPC treatment is symptom control, particularly pain relief, which in turn should result in improved QoL.

At baseline (57/126) 45% had clinically significant moderate to severe pain which improved for 43% by three months. However, over a third with mild or no pain at baseline developed pain that interfered with their work, sleep and enjoyment of life. Our interviews with the men and their partners (manuscript submitted) provides some insight into why pain was such a problem; this included attributing hip and back pain to old age rather than cancer, and limited or no referral to health care professionals for pain management discussions. It is known men are more reluctant to seek help with their symptoms and under-report pain [24], which makes it challenging for the clinician to deal with it effectively.

One study showed that pain prevalence and severity were higher in patients with metastatic prostate cancer with prior docetaxel exposure and that analgesics were underutilised [25].

In EXTREQOL less than 25% of men presented with their first progression to mCRPC, and we have few data on previous lines of therapy to explore this aspect in more detail. Bone pain is a predictive factor for the development of skeletal related events such as a pathological fracture, and patients need to be encouraged to report symptoms early to help circumvent these potential oncological emergencies such as spinal cord compression [26].

Other agents, such as denosumab, have been shown to help relieve bone pain and improve QoL in men with mCRPC, but is not routinely available in the UK [27].

It is common practice to change mCRPC treatment if there are signs of progressive disease, and in EXTREQOL 54% of patients had switched to next line therapies. According to a recent survey of 118 prostate cancer specialists, most clinicians favour clinical progression over prostate-specific antigen or imaging to drive treatment switch decisions [28]. Another recent survey of 109 specialists showed that treatment decisions are also influenced by whether or not patients live alone. [16] In EXTREQOL treatment type did not appear to influence QoL but it was worse for those men where treatment was stopped. The most obvious explanation is that these men had relapsed and were experiencing more symptoms from their disease.

Information was lacking on the impact prostate cancer and its treatments might have on the patient and his family, how to cope at home and access supportive resources. This was made worse by the fact that at six months there was no change in their knowledge. Similar gaps in information provision were identified in a series of studies from Canada in men with advanced prostate cancer. [29-31]. Of course many clinical factors lead to deterioration in health and QoL over time, not only a lack of information or support, but there is strong evidence that low literacy and subsequent low levels of information seeking correlates with poorer health and worse outcomes [32]. In EXTREQOL; men who had an overall better QoL at baseline reported receiving more information about their disease and treatment. These findings may reflect better doctor-patient communication, which is shown to have a strong influence on QoL [33].

The management of mCRPC requires a multidisciplinary team (MDT) approach, with the patient receiving information from different specialties, and it is not unusual for patients to seek the same piece of information from a series of health professionals. This may be because they did not understand it the first time, or want to be sure the message is consistent. Often it is the nurse specialist who covers the largest number of information areas including supportive and psychosocial aspects of care [34]. However, in the realm of

mCRPC, specialist nurses are rare, and MDTs are dependent on the community teams to provide much of the information. UK health care professionals are aware of these shortcomings in patient care, especially in understaffed and busy NHS clinics, where many men with mCRPC are managed in general urological oncology clinics alongside others with a variety of different stages of prostate cancer [16].

Although our study provides real world QoL data for men receiving mCRPC treatments, there are several limitations of the study. These include the relatively small patient sample, lack of medical and prostate treatment history and lack of information about treatment variation and palliative care team support. These prevent detailed interpretation of the results but do not detract from the observation that men with mCRPC outside a trial setting have a poor QoL and inadequate pain control. These circumstances make achieving optimal quality of life and importantly quality of survival for these patients with more complex needs, challenging. Routine use of PROMs in clinics, an increase in advanced nurse specialists, early access to the palliative care and/or pain management teams can surely improve the lives for these patients and their families.

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Conflict of Interest: HP has attended and received honoraria for advisory boards, travel expenses to medical meetings and served as a consultant for AstraZeneca, Astellas, Janssen, Sanofi Aventis, Takeda, Amgen, Ipsen, Ferring, Sandoz and Novartis. HP's work was supported by the UCLH/UCL Comprehensive Biomedical Research Centre. All other authors have no conflicts of interest to declare.

Short Title: EXTREQOL study results revision

Data statement: Data for this study are held at the SHORE-C unit at the University of Sussex and will be made available via the Sussex repository.

FIGURE LEGENDS

Figure 1: Consort Diagram for EXTREQOL

Figure 2: Estimated mean FACT-P, FACT-G and TOI scores with 95% confidence intervals over time using linear-mixed effects models, adjusted for age and whether the patient had a partner

Figure 3a: Baseline plot showing very much /quite a bit scores for INFO25 information needs

Figure 3b: 6 month plot showing very much /quite a bit scores for INFO25 information needs

Table 1: Patient characteristics

	N=132 (%)
Age (years): Mean (SD) Min - Max	73 (7.7) 52-91
Presenting with mCRPC for the first time Yes	30 (23%)
Site of metastasis: Bone Visceral Both Missing	82 (62%) 19 (14%) 29 (22%) 2 (2%)
Treatments discussed at baseline for mCRPC:	
abiraterone	16
abiraterone ; (plus PROMPTS - MRI scanning trial)	1
abiraterone; docetaxel	1
abiraterone; enzalutamide	7
abiraterone; enzalutamide; radium-223	1
abiraterone; radium-223	1
biclutamide	1
biclutamide ; enzalutamide	1
cabazitaxel	5
cabazitaxel; olaparib delivered in the TOPARP Trial	1
cabazitaxel; radium-223, olaparib delivered in the TOPARP Trial	1
cabazitaxel; radium-223	2
docetaxel	21
docetaxel; docetaxel + AZD5363 / docetaxel alone (PROCAID Trial)	4
docetaxel; enzalutamide	5
docetaxel; olaparib delivered in the TOPARP Trial	1
docetaxel: pembrolizumab + chemotherapy (KEYNOTE Trial)	1
dexamethasone	6
enzalutamide	35
enzalutamide; enzalutamide (plus PREMISE observational trial)	3
enzalutamide; radium + enzalutamide / enzalutamide alone (PEACE III Trial)	2
enzalutamide ; radium-223	1
enzalutamide; radium; radium + enzalutamide / enzalutamide alone (PEACE III Trial)	1
radium-223	10
radium-223; radium-223 (plus FASTMAN Trial - tissue sampling)	1
radium-223; radium-223 (plus REASSURE Trial - observational)	2
missing	1

Table 2 shows proportion of patients whose QoL scores declined, improved or remained the same from baseline to 3 and 6 months for the FACT – P total, PCS, TOI and the FACT-G

QoL Measure	Decline		No change		Improve	
	3mths N=118	6mths N=106	3mths N=118	6mths N=106	3mths N=118	6mths N=106
FACT-P	35% (41)	45% (48)	38% (45)	31% (33)	27% (32)	24% (25)
PCS	37% (44)	47% (50)	22% (26)	24% (25)	41% (48)	29% (31)
TOI	51% (60)	58% (61)	11% (13)	13% (14)	38% (45)	29% (31)
FACT-G	34% (40)	40% (42)	42% (49)	41% (42)	25% (29)	20% (21)

Table 3a Clinically meaningful changes in pain intensity (BPI Q3) for patients who had pain intensity (BPI Q3) ≤ 4 at baseline (n=69) and > 4 at baseline (n=57)

	Group 1 None or little pain at baseline (n=69)		Group 2 Moderate/severe pain at baseline (n=57)	
	3mths	6mths	3mths	6mths
Improved	4/63 (6%)	3/58 (5%)	20/47 (43%)	16/40 (40%)
No change	39/63 (62%)	35/58 (60%)	21/47 (45%)	17/40 (42%)
Declined	20/63 (32%)	20/58 (34%)	6/47 (13%)	7/40 (18%)

Table 3b Clinically meaningful changes in interference score (sum of items from BPI Q9) for patients who had pain intensity (BPI Q3) ≤ 4 at baseline (n=69) and those who had pain intensity (BPI Q3) > 4 at baseline (n=57)

	Group 1 None or little pain at baseline (n=69)		Group 2 Moderate/severe pain at baseline (n=57)	
	3mths	6mths	3mths	6mths
Improved	21/69 (30%)	17/69 (25%)	33/57 (58%)	37/57 (65%)
No change	22/69 (32%)	26/69 (38%)	7/57 (12%)	6/57 (11%)
Declined	26/69 (38%)	26/69 (38%)	17/57 (30%)	14/57 (25%)

Table 4: Type of analgesia reported by the patients at each time point

	Baseline (n=132)	3 months (n=118)	6 months (n=106)
no analgesia/not required	39	31	30
paracetamol/ibuprofen	32	28	19
codeine +/- paracetamol/ibuprofen	20	15	16
morphine/ other opioids	27	27	24
other e.g. amitriptyline, naproxen	2	5	3
missing data/ N/A	12	12	14
radiotherapy (received in combination with pain relief medication)	1	1	3
combined drug therapy	49/81 (60%)	42/75 (56%)	38/62 (61%)

Figure 1: Consort diagram – see separate file

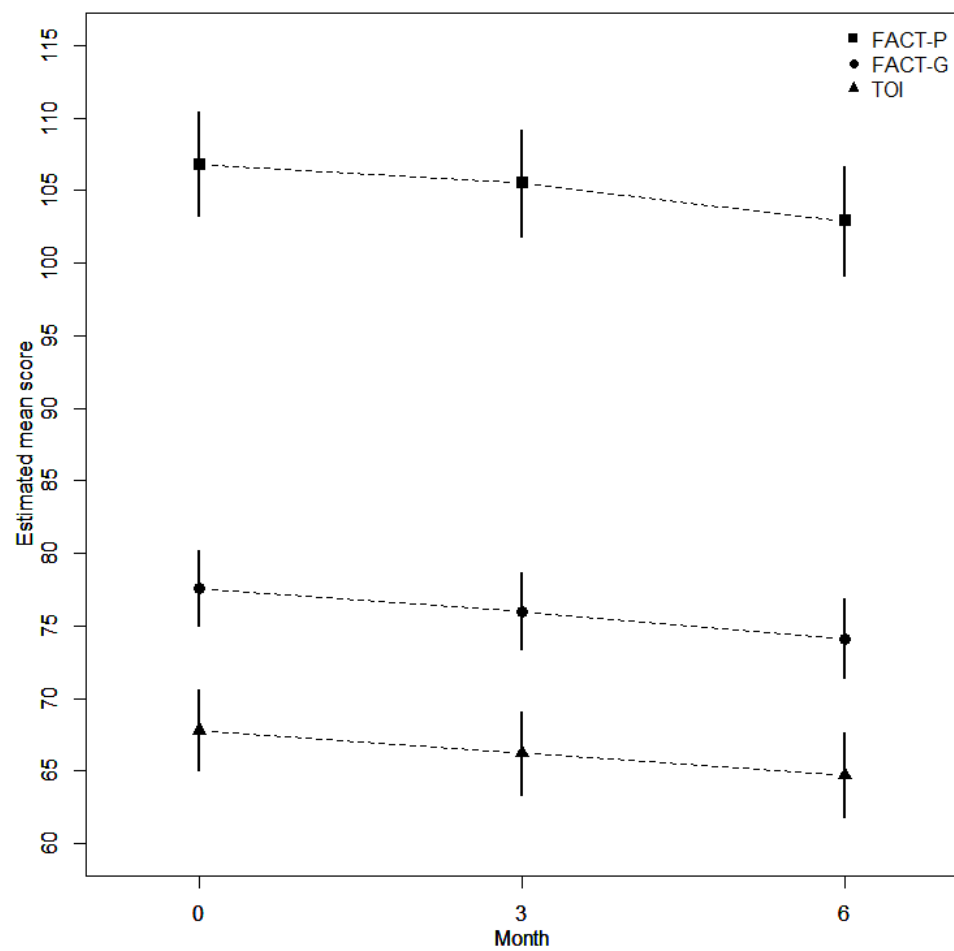


Figure 2:

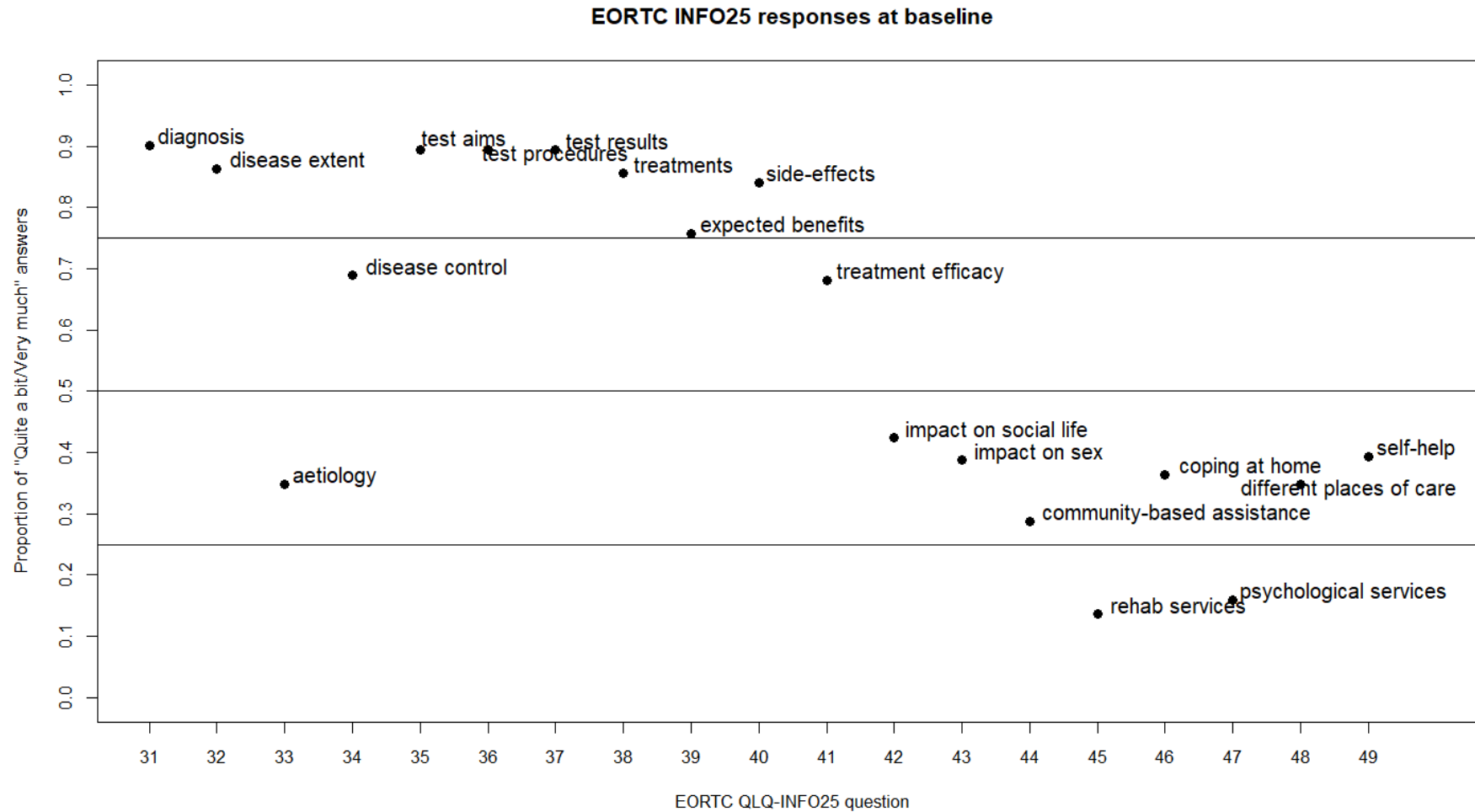


Figure 3a:

Figure 3b:

